EXHIBIT 13

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01/12/2004 05:37:48 PM GMT

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bcc
Subject Re: Compiled comments on the manuscript

Charles,

Please note my additional comments in blue on pages 1 and page 4 (attached)

Page 1 -- Since you said that this registry DOES include bipolar subjects, I would strike the words noted in my "alternative" title suggestion

Also, I thought John Kody's suggestion regarding the title and abstract conclusion were good, and therefore I cut and pasted them (in blue on pages 1 and 4)

Lou

valproate_12_01_03 revised --2.doc

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01/12/2004 09:52 AM

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cc:
Subject: Compiled comments on the manuscript

EXHIBIT 248
WIT:
DATE: 1-14-14
Juliana Zajicek CSR

All,

I think that the following is a summary of the comments to be forwarded to the registry. Please check for content and tone of the communication. I will be sending the comments in on the 14 th (Wednesday) at close of day.

Valproate Monotherapy is a Potent Teratogen in Humans –

The current title of this manuscript draft, "Valproate Monotherapy is a Potent Teratogen in Humans" is not consistent in tone with titles I have seen from this group on other manuscripts and abstracts. The original abstract of this study is entitled, "Evidence of Increased Risk of Birth Defects in The Offspring of Women Exposed to Valproate During Pregnancy; Findings from the AED Pregnancy Registry". There is a considerable difference in the tone and meaning between these two titles, and the rationale for choosing this particular title for the current manuscript draft is unclear. the conclusion of the abstract was that the data "may be a risk factor" The title of the manuscript should be identical to the abstract title.

The previous AED manuscript which described the phenobarbital data on teratogenicity was entitled "The Antiepileptic Drug Pregnancy Registry : A Six Year Experience". The title of this valproate manuscript draft should be reconsidered. Strictly as an example, a title such as "A Prospective Evaluation of the Risk of Congenital Malformations Due to Maternal Exposure to Valproate During the First Trimester of Pregnancy ~~in Women with Seizure Disorder~~" is more reflective of the study, of the data presented, clearly describes the group being evaluated, and reads as more objective.

Or John Kody's suggestion;

Teratagenicity Related to Valproate Monotherapy
(or Utilize original abstract title)

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For the Antiepileptic Drug (AED) Pregnancy Registry[3]

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Abstract

Background: Monotherapy valproic acid (VPA) use during the first trimester of gestation has been associated with an increased risk for spina bifida and other major congenital anomalies in the newborn. However, most studies were these studies or case reports? are hampered by a small number of exposed women and a retrospective design.

Methods: Data were collected by the Antiepileptic Drug (AED) Pregnancy Registry from pregnant women throughout the U.S. and Canada who were taking an anticonvulsant drug. Each woman was interviewed by telephone at enrollment, at 7 months gestation and postpartum. With her written permission, the medical records of each mother and her infant were obtained. The outcome ~~tabulated was~~ of major malformations identified ~~by~~ at or before five days of age. The prevalence of congenital malformations among offspring of monotherapy VPA exposed women was compared to that of women exposed to all other AEDs ("internal comparison group") and to that of the Active Malformations Surveillance Program at Brigham and Women's Hospital ("external comparison group").

Results: Twelve affected cases were identified among 149 VPA exposed women (proportion: 8.1%, 95% confidence interval [CI]: 4.2-13.6%). The prevalence in the internal comparison group was 2.9% (95% CI: 2.0-4.1%; odds ratio: 2.7, 95% CI: 1.6-4.7; $p < 0.001$). Assuming a 1.62% prevalence in the external comparison group, the relative risk to having an affected offspring for VPA-exposed women was 5.0 (95% CI: 2.9-8.6; $p < 0.001$) and continued being statistically significant if the population prevalence rate of birth defects is lower than 5.3%.

Conclusions: VPA is a potent The term "potent" teratogen is used a number of times throughout the manuscript, including in the title and in the "Conclusions" part of the abstract. Is there a standard, accepted measure of what defines a drug to be a "potent" teratogen, as opposed to saying a drug possesses significant risk of

teratogenicity? This seems pertinent however, since the descriptive term "potent" certainly carries with it an added connotation and meaning.teratogen in humans and its use should be reduced to the minimum or substituted by another safer AED.(there is no standard for "safer". No data on other drugs found to be "safer" is available from this registry and it would seem that finding the relative safety of the AED's is the (as of yet not finished) goal of the registry)

John Kody's suggestion

Conclusions: The risk/benefit of VPA use during the first trimester should be actively discussed between a physician and their patient. Teratagenicity, and other side effects need to be considered versus the risk of a breakthrough seizure. Further research into the safety of other AEDs used in monotherapy during pregnancy is warranted. ~~VPA is a potent teratogen in humans and its use should be reduced to the minimum or substituted by another safer AED.~~

Keywords: sodium valproate; teratogenic; embryopathy; birth defects; pregnancy registry; folic acid; neural tube defect

Introduction

It is estimated that approximately 1.1 million women with epilepsy are of childbearing age in the United States and give birth to over 20,000 ~~babies~~ each year (Yerby, 2000). ~~Unfortunately,~~ anticonvulsant drugs taken by pregnant women to prevent seizures are among the most common causes of potential harm to the fetus (Holmes et al., 2001) and thus the risks of therapy need to be weighed against the risks of discontinuation or inadequate antiepileptic therapy. ~~Despite this knowledge~~, there are no current guidelines regarding the best management once a woman with epilepsy becomes pregnant (Mawer et al., 2002; Pennell, 2003). This is due to three main reasons: (1) only a modest number of well-designed prospective studies evaluating the teratogenecity of these drugs have been conducted (references?), (2) despite the potential teratogenicity of some of these drugs, avoidance of generalized tonic-clonic seizures is paramount and the avoidance of all seizures is desirable for the physical wellbeing of the mother and the fetus (Zahn et al., 1998), and (3) most case reports describe children who were exposed to multiple anticonvulsants, making a causal relationship between specific drugs and its adverse effects on the developing fetus questionable (Kozma, 2001).reason 1 and three are data limitations leading to the lack of guidelines; reason 2 is true but not a reason why there are no guidlines

Burton first reported the synthesis of valproic acid in 1882 (Henry, 2003). VPA, also known as dipropylacetic acid, was discovered to have antiepileptic properties in 1963. Clinical trials began in 1964, and the drug became clinically available in the United States in 1978 as an immediate-release formulation (Depakene®, ~~Convulex-capsule®~~) for the treatment of absence seizures. (Convulex is not a US product) In 1983, another formulation, divalproex sodium (Depakote®), was introduced, which is an enteric-coated

stable coordination complex of valproic acid and valproate sodium. Although VPA's mechanism of action has not yet been established, the drug's antiepileptic activity may be related to increased brain concentrations of gamma-aminobutyric acid (GABA). VPA is an 8-carbon 2-chain fatty acid, rapidly absorbed after oral administration, and with a short half life. Over the years, the use of VPA has expanded to include treatment of complex partial and other seizures, prevention of migraine headache, and treatment of acute mania associated with bipolar disorder (Taylor, 2000).

The first case report suggesting teratogenicity of VPA in humans was by Dalens et al. (1980). In 1982, Jeavons summarized the outcomes of 196 pregnancies exposed to anticonvulsants. There were 39 abnormal pregnancies and in 13 of them, the mothers received monotherapy with VPA. Of those 13 cases, there were 3 cases of neural tube defects (NTDs), 4 cases of heart defects, 3 cases with facial abnormalities, 1 case of cleft lip and palate, and 2 cases with abnormal digits. In 1984, DiLiberti et al. coined the term "fetal valproate syndrome (FVS)" to refer to a constellation of minor and major malformations: a pattern of facial manifestations (epicanthal folds, flat nasal bridge, small upturned nose, long philtrum, and thin upper lip), multiple systemic involvement, and central system dysfunction (reviewed by Clayton-Smith and Donnai, 1995). The most common observation ~~is~~ was the presence of neural tube defects (Stanley and Chambers, 1982; Robert and Guibaud, 1982; Robert and Rosa, 1983; Nau et al., 1984; Lindhout and Schmidt, 1986; Oakeshott and Hunt, 1989; Lindhout et al., 1992; Omtzigt et al., 1992). Fetal Valproate Syndrome is variously described in the literature. The risk of having ~~a baby~~ an offspring with an NTD for women taking VPA has been estimated at 2% (Lindhout and Meinardi, 1984), approximately 20 times higher than the background risk in the United States, although it may be as high as 5% at high VPA exposure (Bjerkedal et al., 1982, Omtzigt et al., 1992). Other congenital malformations, such as

congenital heart defects, oral clefts, genital abnormalities, and limb defects have also been reported (Ardinger et al., 1988; Clayton-Smith, Donnai, 1995; Wyszynski and Beaty, 1996; Pandya and Jani, 2000; Rodríguez-Pinilla et al., 2000; Kozma, 2001; Holmes, 2002; Stoll et al., 2003).

We report here the results of a prospective study conducted using data from the North American Antiepileptic Drug (AED) Pregnancy Registry over a 6-year period on the relationship between prenatal exposure to VPA and the presence of major congenital anomalies in the newborns infants.

Materials and Methods

Data were derived from the North American Antiepileptic Drug (AED) Pregnancy Registry, which is an ongoing surveillance system of pregnant women exposed to anticonvulsants (Holmes et al., 2004). By November 20, 2003, the Registry had enrolled 3,442 women from the United States and Canada since its inception six years ago. Women are interviewed at enrollment, at 7 months gestation, and postpartum. Medical records were obtained about the mother's medical history and any malformations identified in the infant. The protocol and criteria for the release of findings were established prospectively by a non-industry external Scientific Advisory Committee. The inform consent to be read and signed by each woman who enrolls in the Registry was reviewed and approved by the Human Studies Committee of the Massachusetts General Hospital in Boston, where the Registry is based

Exposed Participants

Exposed participants were those infants exposed to VPA alone during the first trimester of pregnancy. Infants who were not exposed to VPA during the first trimester of pregnancy or those who were exposed to more than one AED were excluded from the analysis. Elective abortions and stillbirths were included in the denominator. A major malformation was defined as a structural abnormality with surgical, medical, or cosmetic importance (Holmes, 1999). Physical features not considered a major malformation were: 1) minor anomalies; 2) deformations; 3) physiological features due to prematurity, such as undescended testes; 4) birth marks; 5) genetic disorders and chromosomal abnormalities; and 6) any finding by prenatal sonography, such as absence of one kidney, that was not identified by an examining pediatrician; 7) a finding at surgery or autopsy, such as a unilobe right lung, that had not been detected in clinical evaluations. The written descriptions of the findings in the examinations of each infant were reviewed

separately by two Registry dysmorphologists, blinded to exposure status, to determine inclusion or exclusion. Any disagreement was resolved by consensus.

The numbers, (12 or 13) need to be standardized and checked. It is not clear in the manuscript whether there are 12 0r 13 cases. Please refer to article in Ob/Gyn News (May 1, 2003 -- Volume 38- number 9 (Maternal Valproate Use Tied to Major Birth Defects. where Lou cited 9 malformations and 140 vpa monotherapy reports as of 3/2003. Twins is one or 2 reports? The abstract reported the number of malformations in 12 pregnancies (not 13 offspring) We should be consistent.

Comparison groups

There were two comparison groups. The first one was comprised of infants exposed to any monotherapy AED, with the exception of VPA, during the first trimester of gestation and who were ascertained by the Registry. This group is called "internal". In order to minimize selection bias, the mothers of the VPA exposed participants and those of the internal comparison group were included in the study only if they had not been aware of the health status of the fetus (ie, presence or not of a congenital anomaly) at the time of the baseline interview. For the second comparison group (the "external" one), the number of newborns with major anomalies observed among women exposed to VPA was compared with the number of cases expected on the basis of rates from the need reference (Nelson and Holmes, 1989) and other hypothetical rates. It should be noted that both the AED Pregnancy Registry and the Brigham and Women's Hospital prevalence rates exclude Mendelian syndromes and chromosomal abnormalities, as mentioned above ("Exposed Participants").

Statistical methods

Statistical analyses were carried-out with the software Stata, version 8.2 (Stata Corporation, 2003). For continuous data, means and standard deviations were calculated and potential differences were tested with simple linear regression. In the case of ordinal variables, multiple logistic regression was used to obtain odds ratios (OR) and their 95% confidence intervals (CI), and to derive adjusted p values.

Results

From February 1, 1997 through November 20, 2002, 3441 (3442 on page 6) women enrolled in the AED Pregnancy Registry. Close to 57% of these women (*n* = 1961) reported taking an anticonvulsant as monotherapy and had had either a liveborn infant or a pregnancy electively terminated because of a fetal abnormality. VPA monotherapy was used by 236 women (12.0% of 1961). Of these, 149 (or 63% of the women exposed to VPA monotherapy) were unaware of the health status of the fetus at the time of the baseline questionnaire. These women constitute the "VPA-exposed" group.

Twelve cases (including twins – for the abstract it was decided that the twins were 1 preganacy and therefore would be described as 1 – Table 1 includes 12 cases, including the twins) with confirmed major malformations were identified in the VPA-exposed group (proportion: 8.1%, 95% CI: 4.2-13.6%). Table 1 presents clinical and exposure characteristics of these cases. Two of the children (#2321 and #2978) are African American and the 11 remaining are Caucasian. All mothers were taking VPA because of seizures (mean age at first seizure 15 years, range 10 to 21). Participant 1085 mentioned that she had many seizures during the first two trimesters of gestation. Unfortunately, it was not possible to obtain the neurologist's records, as this mother could not explain whether the seizures were convulsive or non-convulsive. Mother 2414 had 2 non-convulsive episodes during the first trimester of pregnancy. The mothers of all 13 (12 – see table 1) cases took either prenatal vitamins/multivitamins or supplemental folic acid in the periconceptional period. Participant 2547, who had a baby with penoscrotal hypospadias, was the only smoker in this group. She smoked 1 pack of cigarettes per day during the periconceptional period.

Twins 1181a (male) and 1181b (female) were dizygotic but concordant for their phenotype (lumbosacral spina bifida). The parents elected to terminate the pregnancy at 18 weeks of gestation, shortly after enrolling in the Registry. Case 3445 had a severe form of congenital heart defect (pulmonary atresia, ventricular septal defect [VSD], and tricuspid valve stenosis) which resulted in death at 12 days after birth. Newborn 2712 had multi-organ anomalies, including a VSD. There was no correlation between dosage and severity of the condition. It seems problematic to describe some defects, but not all fo the cases. Since there was no specific trend other than neural tube disorders, it is meaningful to describe the cases?

Internal Comparison

The prevalence at birth of congenital anomalies among offspring of the 149 VPA-exposed women was compared to that of 1048 women exposed to all other AED monotherapies ("internal comparison"). The two groups are very similar in terms of their demographic characteristics and prenatal exposures (Table 2). The prevalence of major malformations among the internal comparison group was 2.9% (95% CI: 2.0-4.1%). Therefore, ~~there was close to a three-fold increased~~ the risk for having an offspring with a major birth defect for VPA-exposed women compared to those taking other AEDs was calculated to be 2.7 (~~OR: 2.7~~, 95% CI: 1.6-4.7; $p < 0.001$).

I had asked the Valpraote statistics contact within Abbott to verify the Confidence Intervals and she was not able to replicate the numbers without knowing certain details. Please provide the equation (s) used for these calculations. If possible please provide the sample sizes for the external group.

External Comparison

The number of newborns with major anomalies observed among VPA-exposed women was compared with the number of cases expected on the basis of rates from the Active Malformations Surveillance Program at Brigham and Women's Hospital (Nelson and Holmes, 1989) and other hypothetical rates. Assuming a 1.62% population prevalence rate of non-genetic major malformations, the relative risk to having an affected offspring for VPA-exposed women was 5.0, ~~with~~ (95% ~~confidence intervals ranging between~~ CI 2.9 ~~and~~ 8.6 (1-sided p-value < 0.001) or 2 sided (?) and continued being statistically significant if the population prevalence rate of birth defects is lower than 5.3%.

Discussion

The North American AED Pregnancy Registry has previously pubished it's methodology. Since it's inception, one drug (Phenobarbital) has been found to have a statistical association with birth defects which has met publication criteria. As case reports are received into the registry, the registry may be able to comment on the safety of other antiepileptic drugs.

The results of this study indicate that maternal exposure to VPA during the first trimester of gestation increases significantly the risk of major congenital malformations, ~~particularly of multiple congenital anomalies~~ cannot say this – there were 2 reports with multiple anomalies – each report unique. They are also in agreement with previous reports showing that VPA is associated with adverse outcomes more frequently than other AEDs (Omtzigt et al., 1992; Koch et al., 1996; Ohtsuka et al., 1999; Kaneko et al., 1999; Adab et al., 2001; Mawer, 2002). New or rarely reported findings in our patients include severe forms of congenital heart defects (pulmonary atresia and tricuspid valve stenosis ? tetralogy of fallot in table) and multi-organ anomalies (not rare). The risks of teratogenicity in offspring of women exposed to valproate has been previously described and is reflected in the manufacturer's product insert.

Several limitations of this study should also be mentioned. First, the external controls are from the Active Malformations Surveillance Program at Brigham and Women's Hospital in Boston. The details available from the review of each infant's medical records are, on average, more extensive than the information obtained by mail from the registry-enrolled infant's physician. At the time this manuscript was being written, the AED Pregnancy Registry initiated the enrollment of controls collecting information in the same fashion as for anticonvulsant-exposed infants. A second limitation is the fact that

the controls from either the Active malformations Surveillance Program at Brigham and Women's Hospital or those from the AED Pregnancy Registry will not include very many, if any, women with epilepsy (or a mood disorder) who are not being treated with anticonvulsant drugs during pregnancy. As mentioned above, while some studies (Olafsson et al., 1998) suggest that this weakness precludes us from identifying other risk factors for malformations in the offspring of epileptic mothers, others (Nulman et al., 1997; Holmes et al., 2000; Holmes et al., 2001) do not support that hypothesis. Thus, the possibility exists that the results are effected by confounding by indication. The underlying reason for treatment- seizures- may be related to the results. Other potential sources of bias include: 1) selection bias found in any registry, 2) the inability to differentiate seizure type and severity of illness, by drug (treatment bias).

Paragraph Another limitation of this and other pregnancy exposure registries is that initially the only outcome that can be assessed is the frequency of all malformations, not specific malformations, such as spina bifida, a ~~well-known~~ reported consequence of maternal exposure to VPA. To establish correlations, such as a three-fold increase in the occurrence of a malformation with a frequency of 1 in 1,000 (like spina bifida or cleft lip), an unattainable sample of at least 8329 monotherapy VPA exposed infants whose mothers were unaware of the status of their infants at time of enrollment would have to be ascertained to establish this correlation with 80% power (Holmes et al., 2004). ~~Finally, this and other pregnancy individual registries are ill-equipped to study the long term effects of prenatal exposure to AEDs. For example, prenatal exposure to VPA has been associated with autism in two retrospective reports (Williams and Hersh, 1997; Moore et al., 2000). A statistically powerful prospective study would require hundreds of VPA exposed children. Only through a consortium of registries this could be feasible.~~

This registry is not an autism registry and it probably is not necessary to discuss what other outcomes will not be measured

~~The risk of having a baby an offspring with a neural tube defect (NTD) for women taking VPA is has been reported to be about 2 to 5 percent (Bjerkedal et al., 1982; Omtzigt et al., 1992; Lindhout and Mainardi, 1994). Thus, in our sample of 149 VPA exposed women, 3 infants with NTD would be expected. This is the exact number of observed cases with NTDs. The mothers of all twelve cases with congenital anomalies in the VPA exposed group took either multivitamins containing folic acid or folic acid supplements during the periconceptional period. The 3 cases with spina bifida were among the 106 VPA exposed women who took folic acid (prevalence: 2.8%, 95% CI: 0.5 8.0%). In agreement with one previous study (Craig et al., 1999) and a previous analysis of the Registry (Nambisan et al., 2003), there is no evidence of prevention of NTDs in this group by vitamin supplementation.~~ The registry is certainly not powered to analyze whether folic acid treatment is protective

Our understanding of the teratogenic risk due to maternal exposure to AEDs has increased a great deal since Janz and Fuchs first questioned this association in 1964. However, most studies have been hampered by caveats that prevent reaching conclusive results (Betrollini et al., 1985):

1. The rarity of both epilepsy (1.2-7.7 epileptic women per 1000 pregnant women) and congenital malformations (2 to 3% of newborns) indicate that large populations need to be investigated.
2. It is difficult to discern the role of the drugs from that of epilepsy itself or of other genetic and environmental factors associated with epilepsy.

The latter has been disputed by recent studies that showed no significant increase in risk of embryopathy in infants of mothers with epilepsy untreated during pregnancy (Nulman et al., 1997; Holmes et al., 2000; Holmes et al., 2001; Fried et al., 2003). The role of epilepsy in generation of birth defects in this population is open to continued discussion. The previous statement seems to indicate that this issue has been, to some extent, resolved. The former, however, remains a difficult issue. For this reason, pregnancy registries have been promoted and activated in several countries by teams of researchers and drug companies. The main aim of these registries is to enroll a large number of exposed women who could be subjected to prospective monitoring and to a standardized recording of data regarding AED treatment and the occurrence of malformations (Beghi et al., 2001; Holmes et al., 2004). The findings presented here for 149 VPA monotherapy-exposed pregnancies are the most extensive information available, to date, on this drug's risks to the exposed fetus. Other strengths of Registry and of this study are: 1) women enrolled before having any prenatal screening, which reduces the risk of self-selection bias to a minimum; 2) the number of VPA exposed women we were unable to find in order to obtain outcome information on their newborns was low: 9.2%; 3) we obtained detailed information about the pregnancy from the mothers, which is likely to be more complete than that that the mother's prescribing physician would provide; 4) we used precise inclusion/exclusion criteria that defined the potential phenotypes more precisely; 5) the level of cooperation of pediatricians, family practitioners and consultants in providing detailed information on the infant's malformations was excellent.

At a cost of $96.00 per month at 1000 mg/day, divalproex sodium is one of the least expensive AEDs (Adelman et al., 2002). Given its effectiveness in the treatment of epilepsy, migraine, bipolar disorder and, perhaps, certain forms of solid tumors (Henry,

2003), VPA is widely used worldwide. The findings of this study indicate that VPA during the periconceptional period is a ~~potent~~ teratogenic agent, even when taken in conjunction with the recommended doses of folic acid supplementation (0.4 mg daily). Women of childbearing age taking VPA should be advised that high-dose folic acid (4.0 mg-5.0 mg daily) supplementation is recommended (American College of Obstetricians and Gynecologists, 1997; Wilson et al., 2003). This should be taken as folic acid alone, not in a multivitamin format, due to risk of excessive intake of other vitamins such as vitamin A. Their neurologists should also consider reducing their exposure to VPA. Given the current belief that epilepsy *per se* does not represent a risk for increased congenital malformations (Fried et al., 2003), avoidance or reduction in VPA therapy during pregnancy should be warranted. The conclusion does not seem to get to the point that prescribers should evaluate the results in the light of drug benefits. Certainly the avoidance or reduction in dose is not a decision to be made only on the basis of this study, but rather on the basis of a risk benefit assessment performed by the practitioner on each patient receiving AED's. One of the major reasons for the registry to be is to advise prescribers about options. These options will be clearer when the data about this drug and the other AED's is known.

As data are available concerning other drugs in the AED registry, the AED Pregnancy Registry will provide information on their relative safety.

Acknowledgements need to shorten –is it necessary?

The staff of the Registry include a director and teratologist (Lewis B. Holmes, M.D.), an epidemiologist (Diego F. Wyszynski, M.D., M.H.S., Ph.D.; previously, Ellice Lieberman, M.D., Dr.P.H.), a geneticist/dysmorphologist (Joan M. Stoler, M.D.), three neurologists/epileptologists (Edward Bromfield, M.D.; Daniel Hoch, Ph.D., M.D., and Shahram Khoshbin, M.D.), a study coordinator (Maya Nambisan, M.P.H.), a research assistant and interviewer (Ivelisse Santos-Rodriguez), an abstractor and data analyst (Helen Ahn), and a consultant in database programming (John Farrell). In addition, we thank especially the staff who helped to develop the Registry since it began: Kelly Huntington, Elizabeth Harvey, Ph.D., Triptaa Surve, M.P.H., Bridget Riley, Sharon Ng'Ok, Lorrie Walker, Marian Simpson, Fred Sheehan, Amy Cohen, Jonathan Raub, M.P.H., Kristin Morales, Barbara Jennings, M.S.W., Sabrina Petersen, Rachel Alsdorf, Henry Hsu, Amanda Wilson, Adam and Jordan Cusner and Dena Freedman.

Members of the Scientific Advisory Committee: Mark Yerby, M.D. (Chair), Portland, OR; Joseph Bruni, M.D., Toronto, Canada; Allen Hauser, M.D., New York, New York; Margaret Jacobs, Bethesda, MD; Robert Mittendorf, M.D., Dr.P.H., Chicago, IL; Janet Cragan, M.D., Atlanta, GA; Lewis Holmes, M.D. (Director of the Registry), Boston, MA.

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~~Ph.D. (Pfizer Pharmaceuticals).~~ Also, Hoechst-Marion-Roussel was a sponsor for the first two years and UCB Pharma made contributions during two years of the study.

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Table 1. Characteristics of cases with major congenital malformations exposed to VPA during early gestation.

Study Number	Dosage at Conception (mg)	Birth Status	Major Malformation
1085	1000	Live	Tetralogy of Fallot, pulmonary atresia
1181a	Epival 1000	Pregnancy terminated at 18 Weeks	Lumbosacral spina bifida; affected twins
1181b	Epival 1000	Pregnancy terminated at 18 weeks	Lumbosacral spina bifida; affected twins
2118	1000	Live	Atrial septal defect, bicuspid aortic valve
2321	500	Live	Postaxial polydactyly, type B
2364	750	Live	Bilateral inguinal hernia
2414	2000	Live	Multiple congenital malformations (spina bifida, cleft palate)
2547	1500	Live	Hypospadias, penoscrotal location
2712	1250	Live	Multiple congenital malformations (including ventricular septal defect [VSD])
2978	750	Live	Equinovarus club foot deformity
2997	750	Pregnancy Terminated	Bilateral multicystic dysplastic kidneys
3445	250	Neonatal death at 12 days of age	Pulmonary atresia, VSD, tricuspid valve stenosis

Table 2. Comparison of maternal and newborn characteristics of women exposed to valproic acid (VPA) and to all other antiepileptic monotherapy drugs (AEDs) during early pregnancy.

	Valproate (n = 149)	All Other AEDs (n = 1048)	OR (95% CI)
Child Male	80 (53.7)	536 (51.2)	1.11 (0.78-1.56)
Married	77 (76.2)	663 (89.4)	0.85 (0.78-0.93)
Mother's Education			
≤Grade 12	18 (24.0)	96 (18.3)	2.4 (0.9-5.8)
Some College, Junior College Graduate	19 (25.3)	140 (26.7)	1.7 (0.7-4.1)
College Graduate (4-year)	30 (40.0)	186 (35.5)	2.1 (0.9-4.7)
Post College	8 (10.7)	102 (19.5)	Reference
Maternal Age (mean, SD)	29 (6)	30 (5)	1.0 (0.9-1.0)
Gravida (mean, SD)	2 (1)	2 (1)	0.9 (0.8-1.0)
Child Caucasian	123 (83.1)	912 (88.7)	0.6 (0.4-1.0)
Father Caucasian	118 (80.3)	879 (85.6)	0.7 (0.4-1.1)
Age at First Seizure (mean, SD)	13.0 (6)	16.9 (8)	0.9 (0.9-0.9)
Seizures During Pregnancy	33 (24.4)	358 (36.9)	0.6 (0.4-0.8)
Prenatal Vitamins or Multivitamins	115 (78.2)	861 (84.2)	0.7 (0.4-1.0)
Folic Acid Supplement	106 (71.6)	649 (63.8)	1.4 (0.9-2.0)
Cigarette Smoking			
None	119 (79.9)	885 (86.4)	Reference
>None, <1/2 pack	10 (6.7)	55 (5.4)	1.4 (0.6-2.6)
≥1/2 pack, <1 pack	10 (6.7)	31 (3.0)	2.4 (1.1-4.9)
≥1/2 pack, <1 pack	9 (6.0)	42 (4.1)	1.6 (0.7-3.2)
Yes, but unknown	1 (0.7)	11 (1.1)	0.7 (0.1-3.5)
Alcohol			
None	124 (83.2)	801 (78.5)	Reference
Moderate (>none, <5 drinks/week)	18 (12.1)	198 (19.4)	0.6 (0.3-1.0)
≥5 drinks/week	4 (2.7)	13 (1.3)	2.0 (0.6-5.7)
Unknown	3 (2.0)	9 (0.9)	2.2 (0.5-7.3)
Child with Confirmed Major Congenital Anomaly[1]	12 (8.1)	31 (2.9)	2.7 (1.6-4.7)
Child's Birthweight (in grams, mean, SD)[2]	3246 (681)	3366 (608)	1.0 (0.9-1.0)
Child's Length (in cm, mean, SD)[2]	51 (4)	51 (4)	1.0 (1.0-1.1)
Child's Head Circumference (in cm, mean, SD)[2]	34 (2)	35 (3)	0.9 (0.8-1.0)

[1]Confirmed by inspection of medical records or interviews with pediatricians by experienced clinical dysmorphologists.

[2]Excluding stillbirths and fetal deaths.

Finally, we at Abbott had asked a consulting teratologist about the cases and have received this reply. For the sake of completion and thououghness can we address these concerns prior to sending the publication out?

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1) Were karyotypes done on the children with MCA and other syndromes reasonably ruled out? (Cases 2414 and 2712)

2) Was 22q11 FISH done on the child with TOF?

3) The postaxial polydacyty is in a black family. This defect is strongly genetic in blacks. Was family history taken? Was genetic contribution ruled out?

4) What is the gestational age at delivery of 2364 (the inguinal hernia). Was the child intubated and mechanicallly ventilated?

5) For case 2547 the correct term is 'penoscrotal transposition'.

6) Need more description of 2414 and 2712 - the multiple anomaly kids. It is insufficient simply to list the known VPA-associated defects because these are also just simply common things.

The twins with spina bifida are interesting as is the one case of MCA with spina bifida. The rest of the defects are all over the board and they have not sufficiently ruled out other causes. Some of these conditions have alternate causes that are testable or that can be ruled in/out by history. My overall impression is that they are counting anything. Outside the already known associations between VPA and NTD/clefts I don't see any concentration of defects. The individual defects they do list are the common ones.

The numbers would be better served by not lumping all the disparate defects together.

Their initial inclusion/exclusion criteria are muddled. This is probably more the way it is written than actual practice. But, they seem to include findings of some surgical or other internal evaluations but not others. I found that very confusing.

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Please accept these comments as "comments" rather than criticisms.